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| 10/574,031 | 06/20/2006 | Yuntao Wu | 59582(47992) | 8029 |

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| EXAMINER | |
|---|---|
| KINSEY WHITE, NICOLE ERIN | |
| ART UNIT | PAPER NUMBER |
| 1648 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/574,031 | WU ET AL. | |
| | Examiner | Art Unit | |
| | NICOLE KINSEY WHITE | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☐ Claim(s) *1-5,7-19,22,24,31,35 and 48* is/are pending in the application.

4a) Of the above claim(s) *48* is/are withdrawn from consideration.

5)☒ Claim(s) *22* is/are allowed.

6)☒ Claim(s) *1-5,7-19,24,31 and 35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 11, 2009 has been entered.

### *Oath/Declaration*

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because it does not identify the citizenship of each inventor. The citizenship for Yuntao Wu is absent.

### *Specification*

The disclosure remains objected to because of the following informalities: The specification contains blanks at pages 5, 6, 14, 15 and 16.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 35 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that a specific host cell is required to practice the claimed invention. As such, the host cell must be readily available or obtainable by a repeatable method set forth in the specification, or otherwise readily available to the public. If it is not so obtainable or available, the requirements of 35 USC 112, first paragraph, may be satisfied by a deposit of the host cell.

The host cells disclosed in the specification do not appear to be produced from a repeatable process, and it is not apparent if the host cells are both known and readily available to the public. It is noted that pages 6, 14, 15 and 16 of the specification indicate that the host cells have been deposited and applicants have submitted a Data Sheet indicating the deposit of the cells at the NIH AIDS Research & Reference Reagent Program. However, there is no indication in the specification as to deposit number or public availability.

If the deposit was made under the terms of the Budapest Treaty, then a statement, affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, or someone empowered to make

such a statement, stating that the instant invention will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 5, 7-9, 13-18, 24 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saiga et al. (U.S. Patent No. 6,090,783).

The claims are directed to an isolated nucleic acid molecule comprising:

a) a promoter, wherein the activity of the promoter is dependent on the presence of the human immunodeficiency virus (HIV) Tat protein;

b) at least one splice donor site and at least one splice acceptor site;

c) an expressible sequence which is not a wild-type HIV sequence, wherein at least part of the expressible sequence is located in an intron between the splice acceptor site and the splice donor site; and

d) a Rev Responsive Element (RRE) from the human immunodeficiency virus, wherein elements (a)-(d) are operably linked; and wherein the at least one splice acceptor site is contained within the RRE; or a complement thereof.

The claims are further drawn to the isolated nucleic acid construct described above wherein the splice donor and acceptor sites are the HIV D1 and HIV A7 donor and acceptor sites, respectively.

Saiga et al. discloses a gene expression vector comprising a) a promoter, which can be the HIV 5'-LTR, wherein the activity of the promoter is dependent on HIV Tat (see col. 4, lines 4-5; col. 8, lines 57-65; and col. 24, line 63 to col. 25, line 17), b) at least one splice donor site and at least one splice acceptor site (see figure 9 and col. 24, line 63 to col. 25, line 17), c) an expressible non-wild type HIV sequence (e.g., a therapeutic gene, which can be toxic; a reporter gene such as CAT, luciferase, etc.) located between the splice donor and splice acceptor (see col. 4, lines 6-9 and col. 8, line 66 to col. 9, line 17), and d) an RRE from HIV (see col. 9, lines 18-28), wherein the elements are operably linked (see figure 9). The construct can be cloned into an expression vector and transfected into a host cell (see col. 8, lines 47-56).

Saiga et al. does not teach the limitation "wherein the at least one splice acceptor site is contained within the RRE." However, it would have been obvious for one of ordinary skill in the art to place the splice acceptor an any location within the construct as long as the expressible sequence was between the splice donor and splice acceptor and splicing of the expressible sequence occurred in the absence of Rev, as desired. Absent unexpected results, there is nothing special or unique about placing the splice acceptor site within the RRE versus slightly downstream of the RRE.

Regarding claims 4, 5, 7-9 and 15, the choice and placement of splice donors and acceptors within a construct is well within the purview of one of ordinary skill in the art. Therefore, it would have been obvious to one of ordinary skill in the art to select HIV splice donors and acceptors (D1/A7 and/or D4/A5) or any other known splice donor and acceptor to incorporate into the claimed construct and the results would have been predictable. Choosing a particular splice donor and acceptor to include in a construct is routine.

Saiga et al. teaches the use of the CAT and luciferase reporter genes, but not the fluorescent proteins recited in instant claims 15. It is well within the purview of one of ordinary skill in the art to substitute one of the many well known reporter genes for another and the results would have been predictable.

***Response to Arguments***

In the reply dated November 11, 2009, applicants argue that there is no motivation to move the splice acceptor site. All of applicants' arguments have been fully considered and not found persuasive.

Saiga et al. teaches that in the case where the construct is introduced into a non-infected cell, gene expression is suppressed. This occurs because there is no Tat to bind to the HIV promoter and start transcription. Furthermore, therapeutic gene expression is further suppressed by removing the therapeutic gene through splicing at the splice donor (SD) and splice acceptor (SA) sites. On the other hand, in the case of an infected cell, the Rev protein is expressed by the HIV genome, which interferes with the splicing activity via the RRE. Furthermore, by using HIV LTR as a promoter, the expression of the therapeutic gene is further enhanced by the transcription enhancing function of the Tat protein of HIV (see col. 25, lines 3-17).

Thus, the purpose of the splice sites is to remove the therapeutic gene when the construct is in a non-infected cell. It is a mechanism to prevent expression of the therapeutic gene in a cell where it is not needed.

It is obvious and well within the purview of one of ordinary skill in the art to place the splice acceptor site in any location (e.g., at the 3' end of the therapeutic gene, beyond the 3' end of the therapeutic gene, in the RRE, etc.) as long as the primary goal of disrupting gene expression by splicing occurs when desired (e.g., in non-infected cells). Applicants' construct with the splice acceptor site in the RRE produces no different result from the construct of Saiga et al. Again, absent unexpected results, there is nothing special or unique about placing the splice acceptor site within the RRE versus slightly downstream of the RRE.

Claims 1-5, 7-18, 24 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Corbeau et al. (U.S. Patent No. 6,323,019) in view of Hope et al. (U.S. Patent No. 6,136,597) and D'Costa et al. (Journal of General Virology, 2001, 82:425-434) and as evidenced by Saiga et al.

Figure 8B of Corbeau et al. discloses a gene expression vector (pDM128) comprising a) an SV40 promoter, b) at least one splice donor site and at least one splice acceptor site, c) an expressible non-wild type sequence (i.e., CAT gene) located between the splice donor and splice acceptor, and d) an RRE from HIV, wherein the elements are operably linked (see figure 8B). Figure 8B also discloses the 3'-LTR. The construct of Corbeau et al. can be cloned into a vector (see, for example, pDM128) and transfected into host cells (see, for example, col. 17, line 51 to col. 18, line 9).

Figure 8B of Corbeau et al. does not disclose a 5' HIV LTR, specific HIV splice donor and acceptor sites, a packaging signal, or various reporter and therapeutic proteins to be expressed in the construct. However, Corbeau et al. teaches that many promoters are useful, including known inducible and constitutive promoters. One preferred promoter comprises the 5' HIV LTR (see col. 4, lines 13-21). Other promoters that can be used include pol III promoters, pol II promoters, or the natural promoters found in an HIV LTR (see col. 6, lines 52-60). In addition, Hope et al. states that when cloning in mammalian cell systems, promoters derived from the genome of mammalian cells or from mammalian viruses (e.g., the retrovirus long terminal repeat; the adenovirus late promoter; the vaccinia virus 7.5K promoter) may be used (col. 13, lines

8-13). Thus, it would have been obvious to replace the SV40 promoter in figure 8B with the HIV 5'-LTR based on the teachings of Corbeau et al. and Hope et al.

Corbeau et al. does not teach the limitation "wherein the at least one splice acceptor site is contained within the RRE." However, it would have been obvious for one of ordinary skill in the art to place the splice acceptor an any location within the construct as long as the expressible sequence was between the splice donor and splice acceptor and splicing of the expressible sequence occurred in the absence of Rev, as desired. Absent unexpected results, there is nothing special or unique about placing the splice acceptor site within the RRE or slightly downstream from the RRE.

The choice and placement of splice donors and acceptors within a construct is well within the purview of one of ordinary skill in the art. Therefore, it would have been obvious to one of ordinary skill in the art to select HIV splice donors and acceptors (D1/A7 and/or D4/A5) or any other known splice donor and acceptor to incorporate into the claimed construct (in appropriate locations) and the results would have been predictable. Choosing a particular splice donor and acceptor to include in a construct is routine.

Further, the inclusion of a packaging signal is also within the purview of one of ordinary skill in the art. It is well known in the art to efficiently transfer lentiviral constructs to other HIV infected cells, packaging signals are necessary to efficiently package the construct into HIV particles, which then go on to infect other cells, thus delivering the therapeutic or cytotoxic protein to other infected cells (see, for example, D'Costa et al.).

Corbeau et al. teaches the use of the CAT reporter gene, but not the fluorescent proteins recited in instant claims 15 and 16 or a therapeutic protein as recited in claims 17 and 18. It is well within the purview of one of ordinary skill in the art to substitute one reporter gene for another or to substitute a therapeutic/toxic gene and the results would have been predictable (see, for example, Saiga et al.).

***Response to Arguments***

In the reply dated November 11, 2009, applicants argue that there is no motivation to move the splice acceptor site. All of applicants' arguments have been fully considered and not found persuasive.

Corbeau et al. discloses a functional assay to assess Rev function. The assay used plasmid pDM128, which contains RRE and the CAT gene in an intron (FIG. 8, panel b). In the absence of Rev, cells transfected with pDM128 express only cytoplasmic spliced transcripts and do not produce CAT protein. In the presence of rev, unspliced RNAs enter the cytoplasm, and CAT is synthesized. (see col. 38, lines 15-22).

Thus, the purpose of the splice sites is to remove the heterologous gene when the construct is in a non-infected cell (no Rev or Tat present). It is a mechanism to prevent expression of the therapeutic gene in a cell where it is not needed.

It is obvious and well within the purview of one of ordinary skill in the art to place the splice acceptor site in any location (e.g., at the 3' end of the therapeutic gene, beyond the 3' end of the therapeutic gene, in the RRE, etc.) as long as the primary goal of disrupting gene expression by splicing occurs when desired (e.g., in non-infected cells). Applicants' construct with the splice acceptor site in the RRE produces no

different result from the construct of Corbeau et al. Again, absent unexpected results, there is nothing special or unique about placing the splice acceptor site within the RRE versus slightly downstream of the RRE.

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Saiga et al. or Corbeau et al. and further in view of D'Costa et al. (Journal of General Virology, 2001, 82:425-434).

The claim requires the inclusion of an internal ribosome entry site (IRES) in the construct.

It would have been obvious to one of ordinary skill in the art to modify the construct taught by Saiga et al. or Corbeau et al. to include an IRES, especially if one contemplates a construct with more than one expressible gene product. One would have been motivated to do so given the fact that IRES sequences are routinely used in the art to allow for the independent initiation of translation of a cloned gene. There would have been a reasonable expectation of success given the fact that there are many others who have successfully created constructs that included IRES (see, for example, D'Costa et al.). Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

***Response to Arguments***

In the reply dated November 11, 2009, applicants argue that there is no motivation to move the splice acceptor site. This argument has been addressed above.

***Allowable Subject Matter***

Claim 22 is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to NICOLE KINSEY WHITE whose telephone number is (571)272-9943. The examiner can normally be reached on Monday through Friday from 9:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Patrick Nolan can be reached on (571) 272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nicole Kinsey White/
Examiner, Art Unit 1648

/Stacy B Chen/
Primary Examiner, Art Unit 1648